[C A S E   R E P O R T   A N D   L I T E R A T U R E   R E V I E W]

Generalized Anetoderma after Intravenous Penicillin Therapy for Secondary Syphilis in an HIV Patient

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ABSTRACT

Anetoderma is a rare, benign disorder characterized microscopically by the pan-dermal loss of elastic fibers in the dermis and presenting clinically as circumscribed, skin-colored or grey-white atrophic macules and/or patches on the trunk and/or extremities. Lesions are described as having a "sac-like" appearance, since they bulge or herniate upon palpation. Although the clinical picture is characteristic, a definitive diagnosis requires histological confirmation in order to differentiate this disorder from other conditions of elastolysis, such as cutis laxa and mid-dermal elastolysis. Little is known concerning the pathogenesis of this condition, and treatment attempts have been both diverse and unsuccessful. This article will review a case of generalized anetoderma in a patient with secondary syphilis after being treated with intravenous penicillin, along with a concise literature review. (*J Clin Aesthet Dermatol.* 2013;6(8):23–28.)

A 43-year-old Caucasian man with a history of human immunodeficiency virus (HIV), receiving highly active antiretroviral therapy (HAART) for seven years, presented to the outpatient dermatology clinic with complaints of "spots" all over his body. Two months prior, during an admission to the hospital for the treatment of secondary syphilis with intravenous penicillin, his skin lesions began to appear. They started on his left arm as red, itchy "bumps" that quickly spread in size and number to affect his trunk and extremities. The patient reported that his scalp, palms, soles, face, and mucous membranes were spared. He also denied any prior skin complaints, change in medications, drug abuse, or recent sexual activity. Physical examination demonstrated numerous skin-colored to white macules with a wrinkled surface on the trunk and extremities (Figure 1). The macules followed skin-cleavage lines and protruded upon forward bending, but disappeared upon lying down (Figures 2A and 2B).

An atrophic macule from the right arm was biopsied. Hematoxylin and eosin (H&E) staining demonstrated a perivascular lymphoplasmacytic infiltrate (Figures 3A and 3B). Verhoeff Van-Gieson (EVG) elastin stain showed absent and fragmented elastic fibers in the dermis, and a Masson's trichrome stain demonstrated no abnormalities in collagen or smooth muscle (Figures 4A and 4B). Immunohistochemical staining for antitreponemal antibodies was negative. Serum testing for antinuclear antibodies, thyroid autoantibodies, thyroid function, antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody), and complement levels were all within normal limits. Rapid plasma reagin (RPR) was positive at a titer of 1:240 despite intravenous penicillin treatment in the recent past. Thus, the clinical findings in conjunction with microscopic analysis and negative blood examination confirmed a diagnosis of anetoderma in the setting of HIV and secondary syphilis.

DISCUSSION

Introduction. Anetoderma, first described by Jadassohn in 1892, is a rare cutaneous disorder characterized by localized areas of elastolysis.[1] Histological examination of lesions demonstrates focal loss of elastic fibers in the superficial and mid-dermis, which manifests clinically as a herniation phenomenon in the affected areas.[2] The classic presentation is that of multiple and well-circumscribed "sac-like" macules and/or patches with a predilection for the

Figure 1. Up-close view of multiple, well-circumscribed, wrinkled-appearing macules following skin cleavage lines on the left trunk and extremity.

Figures 2A and 2B. A) Herniation of macules upon forward bending and B) their disappearance upon lying flat.

chest, back, neck, and upper extremities.

Historically, idiopathic lesions of anetoderma were classified clinically as either inflammatory (Jadassohn-Pellizzari type) or non-inflammatory (Schweninger-Buzzi type), although both types of lesions may be found in the same patient. This classification has since been abandoned. Interestingly, there is no concordance between the clinical and pathological findings in these two groups, as peri-vascular infiltration of inflammatory cells is present in all anetoderma lesions no matter the clinical appearance.[2]

Current classification separates lesions into primary and secondary types, where the former represents an idiopathic occurrence of atrophic lesions in areas of skin that appear normal prior to the onset of atrophy. Various autoimmune, ocular, bony, cardiac, and other extra-cutaneous abnormalities have been reported in patients with primary anetoderma.[3] Associations in the literature with lupus erythematosus, autoimmune thyroiditis, and antiphospholipid antibody syndrome should prompt clinical and laboratory searches for an autoimmune disorder in any patient presenting with primary anetoderma.

Secondary anetoderma implies lesions which occur in areas of previous or current skin pathology, and has been described with many conditions including acne, acrodermatitis chronica atrophicans, insect bites, varicella, syphilis, leprosy, tuberculosis, granuloma annulare, and urticarial pigmentosa.[4-5] An underlying systemic disease may accompany both forms, although whether these findings are coincidental or related has yet to be elucidated.[6-7] The authors' patient had underlying HIV, with anetoderma lesions occurring within areas of secondary syphilis as well those arising in areas lacking prior skin pathology.

Etiology. The pathogenesis of anetoderma remains unknown, despite many reported associations and causes. Loss of elastic fibers may be explained by defective synthesis, increased activity of elastolytic enzymes, or autoimmune-mediated destruction of fibers.[8] Most investigations have focused on the latter two possibilities.

Extracellular matrix integrity is largely maintained through a careful balance of two enzymatic families: matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[9] One recent study assayed the expression of MMP and TIMP family proteins in samples of anetodermic skin and found elevated levels of several members of the MMP family that act to degrade elastin.[10] This elevation was unaccompanied by an equivalent increase in TIMP levels, suggesting a focal imbalance of elastolytic enzymes and their inhibitors that favors an environment of fiber breakdown.[10] Further, recent evidence has implicated MMP dysregulation in HIV infection, suggesting that the pathogenesis of HIV-associated skin lesions may be partially due to abnormal remodeling of matrix proteins.[9,11] Given its strong association with both primary and secondary anetoderma in the literature, the pathophysiological consequences of HIV infection on the skin warrants further investigation.[6]
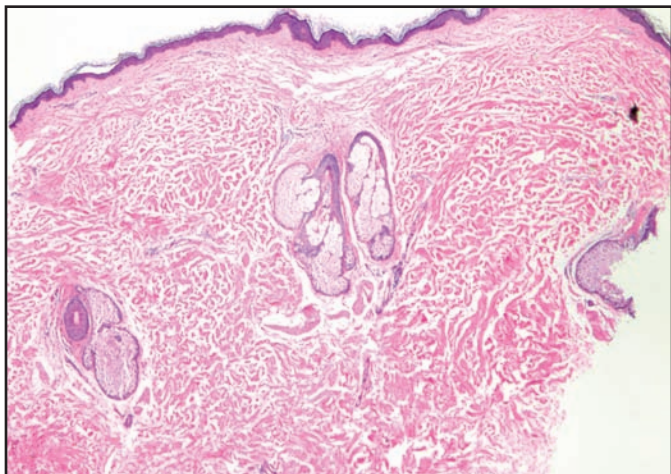
Figure 3A. Superficial perivascular dermatitis, seen at low magnification (H&E, 2x)
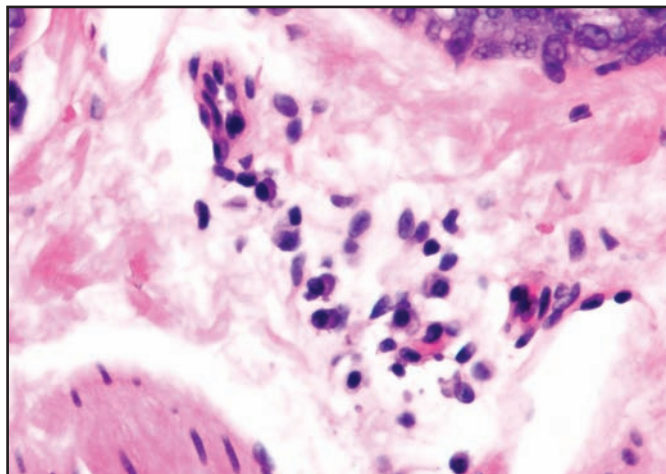
Figure 3B. Lymphoplasmacytic infiltrate seen in the papillary dermis (H&E, 40x)
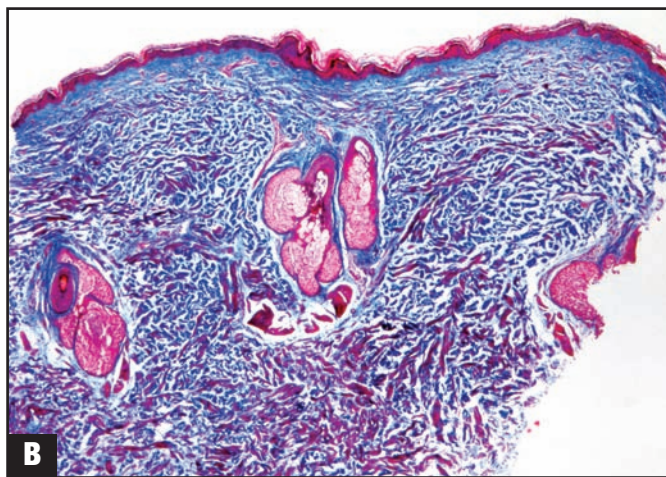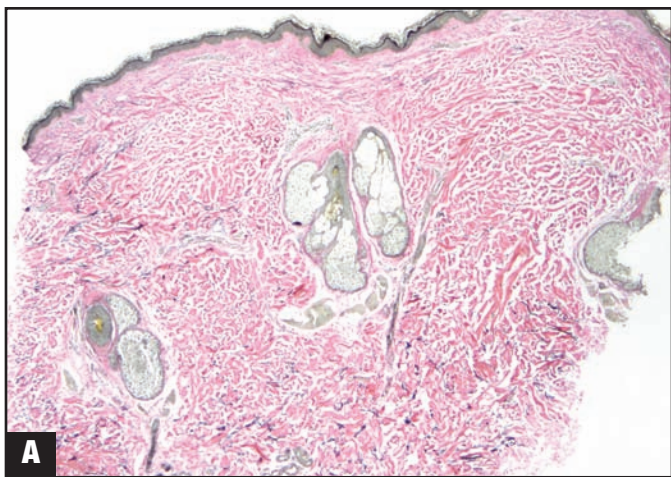
Figures 4A and 4B. Special staining shows A) an absence of elastic fibers in the papillary and mid-reticular dermis (EVG, 2x) and B) no collagen (blue) or smooth muscle (red) abnormalities (Trichrome, 2x).

A substantial body of literature associates anetoderma with the presence of antiphospholipid antibodies and other serological markers of autoimmunity.[7,12–17] Positive immunofluorescence has been reported in lesional skin of anetoderma, with granular deposits of immunoglobulin M (IgM) and C3 at the dermoepithelial junction, between collagen fibers in the dermis, and on residual elastic fibers.[18] Additionally, electron microscopy has demonstrated fragmented elastic fibers present within macrophages, further implicating an immunological mechanism.[8] Several studies have subsequently linked anetoderma with concurrent Graves' disease (autoimmune thyroiditis), lupus erythematosus, autoimmune hemolysis, systemic sclerosis, and alopecia areata, strengthening the clinical association between anetoderma and autoimmunity.[12–13]

As mentioned earlier, of specific importance is the presence of elevated antiphospholipid antibodies in patients with anetoderma. This association was first noted in a study of five patients who were all positive for anticardiolipin antibodies, two of whom were also positive for antinuclear antibodies.[19] Subsequent studies have published a combined 26 additional patients who were all positive for various antiphospholipid antibodies.[13,16,20] Interestingly, one case showed a patient to be negative for antiphospholipid antibodies, but positive for anti-thyroid peroxidase.[7] The summation of these studies has influenced many researchers to view anetoderma as a cutaneous manifestation of autoimmune disease,[7,13] and has prompted at least one investigator to also suggest evaluating patients with primary anetoderma for autoimmune disease.[14]

Clinical presentation. Typical lesions are characterized by well-circumscribed, atrophic, flesh-colored or white macules and/or patches, measuring up to a few centimeters in diameter and with a wrinkled or centrally depressed appearance. Often, lesions will follow relaxed skin tension lines or skin cleavage lines on the trunk or extremities,

TABLE 1. Disorders of elastic tissue*

CONDITION	CLINICAL FINDINGS	PREDILECTION	PATHOLOGY
Anetoderma	Multiple circumscribed areas of flaccid skin	Trunk	Focal loss of elastic fibers in the papillary and/or mid-reticular dermis
Mid-dermal elastolysis	Diffuse areas of fine wrinkling and occasional perifollicular papules	Trunk, arms, lateral neck	Band-like loss of elastic fibers in the mid-dermis
Cutis laxa	Loose, sagging skin folds resulting in prematurely aged appearance	Eyelids, cheeks, neck, shoulder, girdle, abdomen	Reduced and fragmented elastic fibers throughout the dermis
Pseudoxanthoma elasticum	Yellowish coalescing skin papules, "cobblestoning," and redundant folds in flexural sites	Lateral neck, axillae, groin	Calcified and clumped elastic fibers in the mid-dermis
Elastosis perforans serpiginosa	Small keratotic papules arranged in arcuate or serpiginous patterns	Lateral neck, antecubital fossae	Thickened elastic fibers are extruded from the dermis through a transepidermal channel

*Adapted from: Bolognia JL, Jorizzo JL, Rapini RP. *Dermatology.* 2nd ed. London: Mosby Elsevier; 2008.

sparing the face, palms, and soles. The macules and/or patches may depress upon palpation ("buttonhole" sign) or appear to herniate outward, especially upon forward bending. Lesions may be few or numerous, and predicting the clinical course based on exacerbated or newer-appearing lesions is difficult. In cases of secondary disease, lesions will follow the primary underlying dermatosis and may manifest as inflammatory papules, wheals, vesicles, or scaly plaques (polymorphic) prior to the typical clinical appearance of a scarred macule or patch.

Diagnosis. A definitive diagnosis can only be determined with microscopic analysis of lesional skin, although the clinical finding is characteristic in the majority of cases. Histological sections demonstrate a loss of elastic fibers in the mid-reticular and/or papillary dermis.[2] Focal loss of elastin correlates with the clinical observation of atrophy and "buttonhole" sign. A perivascular inflammatory infiltrate is present, and may be of multiple cell lineages. A study of 34 biopsies across 15 patients with anetoderma observed that lymphocytes were the predominant cell type, with secondary inflammatory cell components of histiocytes, plasma cells, and eosinophils, in descending order of prevalence.[2] It is notable that inflammatory cells are present in all biopsies regardless if the lesions appear clinically inflamed, and that the secondary cell-type variation has yet to be correlated with any of the patients' underlying conditions.

Differential diagnosis. Anetoderma must be differentiated from other elastic tissue disorders (focal dermal atrophies and conditions) that mimic the herniation phenomenon seen clinically, often requiring the combined clinical and microscopic appearance of these lesions for diagnosis (Table 1).[21] A similar entity, mid-dermal elastolysis, often presents with larger and more diffuse areas of skin wrinkling. In this case, elastic fibers are lost in the mid-dermis, with only a rare lymphohistiocytic inflammatory infiltrate present around adnexal vessels.[22] In contrast, cutis laxa manifests as wrinkled folds or lax skin in large areas, and biopsies show a significant loss of elastin throughout the entire dermis.

The major clinical differential is between post-traumatic scars and papular elastorrhexis. This latter entity is a rare cutaneous disorder in adolescents, consisting of multiple white or skin-colored indurated papules. The histological findings are similar, with absent and fragmented elastic fibers in the superficial dermis, but the clinical presentation differs from anetoderma.[23,24] While lesions typically share a similar distribution as anetoderma, on the

trunk and extremities, they are only 0.1 to 0.5cm in diameter, firm to palpation, and lack any herniation phenomenon.

Treatment and management. There is no satisfactory treatment for anetoderma at the present time. Administration of topical and oral corticosteroids, penicillin, aspirin, phenytoin, dapsone, topical and oral vitamin E, and oral niacin has all yielded meager results.[2] Additional studies have reported potential improvements following treatment with colchicine and aminocaproic acid (a lysine derivative that may work through regulation of proteolytic enzymes), although early treatment would be warranted for a greater chance of success.[25,26] As of yet, no method is curative or helps to predict the final disease outcome.

Recently, one report in the literature described the successful treatment of anetoderma lesions secondary to Stevens-Johnson syndrome using ablative CO_2 (10,600nm) fractional laser technology.[27] Ablative lasers are commonly employed in cosmetic skin rejuvenation procedures, demonstrating great success in improving fine or deep wrinkle lines through the principle of collagen remodeling. Heat directed into the dermis damages hydrogen bonds in the collagen triple helix, and the resultant inflammatory and remodeling cascades help to rebuild a stable configuration that manifests as improved texture, increased skin tightening, and decreased skin wrinkling.[28,29] Unfortunately, dermal heating using ablative technologies initiates a wound healing response that takes longer to complete than with nonablative technologies, and the downtime is much more significant. However, there is evidence indicating that both collagen and elastin fibers are regenerated during this process.[30]

A newer fractional technology with radiofrequency (RF) works on the same principle of dermal heating, but delivers dermal heat without compromising the epidermis.[31–33] In one study of this device, pre- and post-procedure biopsies of normal and treated abdominal skin were stained with EVG and anti-elastin antibodies, demonstrating a significant increase in elastin content in the zone of thermal injury.[30] Given the strictly dermal pathology without epidermal change in the setting of anetoderma, nonablative fractional RF technology may represent a beneficial treatment with little downtime if it is able to increase dermal protein content. Future studies may help to assess this device as a treatment option.

Fillers, such as silicone, poly-L-lactic acid, and hyaluronic acid derivatives have been used to treat depressed acne scars and may be useful in treating lesions of anetoderma. In addition, trichloroacetic acid (TCA) peels or other rejuvenation procedures, such as dermabrasion, are thought to induce cell turnover and stimulate collagen production through tissue remodeling, which may prove cosmetically effective for patients with anetoderma.[34–38]

CONCLUSION

Anetoderma is a rare condition characterized by focal areas of dermal elastolysis. Lesions may be primary or arise secondary to prior skin pathology, and both forms may coexist on the same patient. Despite growing inquiry into its pathogenesis, the etiology remains unclear, and no treatment has proven curative. Resurfacing with ablative or newer fractional laser or RF systems may provide some benefit, although only a single case report has been published to date. The authors' case report and review highlights the importance of increasing disease awareness in order to properly guide treatment and management.

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